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(54) Aqueous concentrate for dialysis solutions.

(57) In order to obtain storable and bacteriostatic concentrates for dialysis solutions having, if any, small contents of acetate, the concentrates according to the invention are divided to two containers one of which contains an aqueous solution (A) of sodium carbonate or bicarbonate and the other of which contains an aqueous solution (B) of an acid forming physiologically compatible sodium and calcium salts as well as calcium cations and optionally magnesium cations, whereby both solutions (A) and (B) may contain additionally sodium chloride and, if desired, potassium cations.

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Aqueous Concentrate For Dialysis Solutions

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It is known to use haemo dialysis solutions which contain sodium bicarbonate together with sodium chloride and optionally other alkali and alkali earth chlorides. But there has been found as disadvantage of such dialysis solutions containing bicarbonate that calcium and magnesium carbonates may precipitate. In order to avoid these disadvantages, different methods have been used.

One method was to replace sodium acetate for the bicarbonate since the alkali earth acetates are easily soluble, so that no precipitates of slightly soluble calcium or magnesium compounds result. But since the acetate is partly transferred into the blood, sometimes the patients show acidosis which makes undesirable the use of acetate instead of bicarbonate in haemo dialysis solutions. Another method was that, to bubble carbon dioxide into the dialysis solution in order to maintain the pH value of the dialysis solution in the acidic range and to suppress the formation of slightly soluble magnesium and calcium carbonates. But bubbling carbon dioxide into a dialysis solution is a process complicated and capable of interferences, and in this method the introduced amount of carbon dioxide and thus the pH value can be controlled only relatively bad.

Additionally the physicians prefer storable concentrates for dialysis solutions which concentrates have only to be diluted by water to become useful. But concentrates of aqueous sodium bicarbonate solutions containing calcium ions are not stable and only slightly bacteriostatic.

The object of the invention was to obtain concentrates for dialysis solutions which are storable and bacteriostatic, also in their final composition, and thus may be left standing for some time without the necessity of bubbling carbon dioxide into the solution. Moreover the dialysis solutions shall contain at most slow amounts of acetate.

The inventive aqueous concentrate for dialysis solutions containing sodium chloride, carbonate or hydrocarbonate, respectively, calcium cations and optionally magnesium and/or potassium cations is characterized in that it is divided to two containers one of which contains an aqueous solution (A) of sodium carbonate or bicarbonate and the other of which contains an aqueous solution (B) of the calcium cations and, if magnesium cations are contained, of the magnesium cations, as well as of an acid which forms

physiologically compatible sodium, calcium and optionally potassium and magnesium salts.

According to the first embodiment of the invention the solution (A) contains sodium carbonate and the solution (B) contains hydrochloric acid as the acid.

It is unusual to use strong acids such as hydrochloric acid in physiological aqueous solutions. But the said acid is immediately reacted when combined with the aqueous solution containing the sodium carbonate, whereby sodium chloride is formed. During that reaction the sodium carbonate forms the equivalent amount of sodium bicarbonate, and in the event of a corresponding proportionation of the amount of hydrochlorid acid, a smaller part of the said sodium bicarbonate is decomposed to form additional sodium chloride and carbon dioxide which has the function of the carbon dioxide which is usually bubbled into the solution and adjusts the pH value of the dialysis solution.

Thus since the hydrochloric acid contained in the solution (B) serves on the one hand completely to convert the sodium carbonate to sodium bicarbonate and on the other hand to decompose a smaller portion of the formed sodium bicarbonate forming carbon dioxide, it is preferred that the solution (B) contains 1,05 to 1,3, preferably 1,05 to 1,2 mole of HCl per mole of Na_2CO_3 in the solution (A). One mole of the said hydrochloric acid is necessary to convert quantitatively the sodium carbonate to sodium bicarbonate, whereas the remaining amount of hydrochloric acid serves to release CO_2.

The amount of sodium chloride formed during the said reactions may be calculated, so that there is added to the solutions (A) and/or (B) the amount of sodium chloride necessary for the dialysis solution, less the amount of sodium chloride formed in the above reactions. The said sodium chloride which is necessary in the dialysis solu-

tion to make it substantially isotonic with the blood liquid, may be added to each of the both solutions (A) and (B) or partially to both. Additionally there are added calcium chloride and optionally magnesium chloride and potassium chloride to the concentrate in the usual manner. The amounts of these compounds in the dialysis solutions are known and are not distinguished from the prior art. However, it is suitable to have in the solution (A) only sodium carbonate, but in the solution (B) additionally to the hydrochloric acid all other compounds, since then the solution (A) may be used as standard stock solution for solutions (B) having different concentration, if only the concentration of hydrochloric acid thereof is in conformity with the concentration of sodium carbonate in the solution (A) corresponding to the above statements.

Since smaller amounts of acetate are not dangereous, it is also possible to replace acetic acid for a smaller portion of the hydrochloric acid.

For example per mole of sodium carbonate in the solution (A) 1 mole of HCl and 0,05 to 0,3 mole of acetic acid should be present in the solution (B).

According to a second embodiment of the invention the solution (A) contains sodium bicarbonate.

It is surprising that the sodium bicarbonate solutions designated as aqueous solution (A) are stable during long time storage and result in stabel dialysis solutions without bubbling carbon dioxide into the solutions to stabilize them.

For this effect it is sufficient that only relatively small amounts of an acid which forms the stated physiologically competable alkali and alkali earth salts are used. This results in the advantage for example in the event of the use of acetic acid, that the ready dialysis solution may

contain only small amounts of alkali acetate which do not result in acidosis. Preferably the aqueous solution (B) contains 0,01 to 0,25, especially 0,03 to 0,15, such as for example about 0,05 mole of the stated acid per mole of sodium bicarbonate in the aqueous solution (A).

By the combination of the two solutions (A) and (B) and with dilution water the hydrogen ions react with a small part of the sodium bicarbonate forming CO_2 which remains in the dialysis solution and stabilizes it by avoiding a formation of alkali earth carbonates and by adjusting the pH value of the dialysis solution.

As acid in the aqueous solution (B) inorganic or organic acids may be used, which form physiologically compatible sodium and calcium salts and, if the aqueous concentrates contain magnesium and potassium cations, form physiologically compatible magnesium and potassium salts, too. Such acids which may be used according to the invention are for example acetic acid, citric acid, lactic acid, hydrochloric acid and/or amino acids.

Acetic acid is preferred among the said acids, if sodium bicarbonate is used in the solution (A). The said acetic acid may be used without hesitation, since the amount thereof is relatively small in comparison with the amount of hydrocarbonate, so that from the dialysis solution only neglectible amounts of acetate can be transferred into the blood of the patient, so that no risk of acidosis exists.

The sodium chloride may be contained in both aqueous solutions (A) and/or (B), but it is preferably present in the solution (A) in a concentration as high as possible. The sodium chloride increases the autosterility of the aqueous solutions. If the aqueous solution (A) contains a great portion of sodium cations, by different dosage of the relative amount of the solution (A) at the combination with the solution (B) and with dilution water, optional

millival values for the sodium in the dialysis solution may be adjusted without having stock solutions of different concentrations. That by the superdosage or underdosage relating to the solution (A) also the other components, such as sodium bicarbonate, are super or under dosed, is no disadvantage , since the bicarbonate is rapidly decomposed by the body.

It may be suitable, if the aqueous solution (B) contains additionally glucose. The amount of the glucose in the solution (B) is suitably 5 to 400 gs/l, preferably 15 to 80 gs/l.

An increased storage stability of the concentrates according to the invention is obtained, if the solution (A) is maintained in a container and under such conditions, that no or only small escape of CO_2 from the solution and the gaseous phase above the said solution out of the said container is possible. This may be reached in a different manner. For example the container can be manufactured of a material or with such a thickness of the wall that no CO_2 or only a very small amount of CO_2 escapes from the solution through the wall of the container. Another suitable method is to store the solution (A) in comparably big containers, so that the ratio of the volume to the surface area of the liquid body is relatively great. Thereby the interface between the solution and the wall of the container, where CO_2 may escape by diffusion, is relatively small in comparison with the volume of the solution. This is especially important, if for the storage of the solution plastic containers must be used for which a diffusion of CO_2 through the wall of the container cannot be excluded. It is surprising that by the choice of big storage containers the bicarbonate solution (A) remains completely stable for long periods of time. The stability of the said solution can still be improved by a storage at low temperatures.

In a surprising manner the solutions are unstable, if they contain too much unbound CO_2 at the time of filling into the containers, since then the containers inflate. This is avoided by the invention.

The aqueous concentrates for dialysis solutions according to the invention have several important advantages over known concentrates for the same purpose. A first advantage is that the solutions are completely stable at the storage during a long period of time as well as at a longer storage during the use without the precipitation of slightly soluble alkali earth compounds and without turbidity.

Another advantage is that by the concentrates according to the invention dialysis solutions are obtained which do not result in any physiological disadvantage such as acidosis.

Finally a high autosterility and a good flexibility of the dosage are obtained, so that optional sodium concentrations in the dialysis solution may be adjusted without having stock solutions of different concentration.

In the practical use both aqueous solutions (A) and (B) are mixed together and with the dilution water separately from the dialysis device or within the dialysis device immediately before the membrane, whereby suitably the solution (A) is diluted with water and then the solution (B) is metered. This may be done suitably by forced dosage in order to adjust the correct ratio of both solutions (A) and (B), whereby in the mixing device the solution obtains the necessary tempereature. Moreover as safety precaution a conductivity and optionally a pH value, density- and/or flow control device may be provided. If desired, the feed of the solutions (A) and/or (B) may be made dependent from the above mentioned measured values, and by these measurements the feed may be controlled.

Example 1

Solution (A):

water 1 l
$NaHCO_3$ 132,3 gs (1575 mmole)
sodium chloride 61,36 gs (1050 mmole)
filling up with water to a total volume of 2 l

Solution (B):

Water 0,5 l
acetic acid 10,517 gs (175 mmole)
NaCl 122,72 gs (2100 mmole)
KCl 5,227 gs (70 mmole)
$MgCl_2.6H_2O$ 7,116 gs (35 mmole)
$CaCl_2.6H_2O$ 13,42 gs (61,25 mmole)
filling up with water to a total volume of 1 l

During the combination of both aqueous solutions there has been diluted with 32 l of water to totally 35 l of dialysis solution. This solution contained 5 mmole CO_2, and in a surprising manner this amount was sufficient to maintain the dialysis solution stable during storage for a longer time, too.

Example 2

Solution (A):

Water 1000 l
Na_2CO_3 water-free 211,47 kg
filling up with water to a total volume of 1500 l

Solution (B):

water 750 l
NaCl 181,0 kg

HCl, 37%ig, 212,1 kg
$MgCl_2.6H_2O$ 10,674 kg
$CaCl_2.6H_2O$ 20,13 kg
filling up with water to a total volume of 1500 l

1 Patent Claims

1. An aqueous concentrate for dialysis solutions containing sodium chloride, carbonate or hydrocarbonate anions respectively, calcium cations and optionally magnesium and/or potassium cations, characterized in that it is divided to two containers one of which contains an aqueous solution (A) of sodium carbonate or bicarbonate and the other of which contains an aqueous solution (B) of an acid which forms physiologically compatible sodium, calcium and optionally potassium and magnesium salts, of the calcium cations and, if magnesium cations are contained, of the magnesium cations.

2. A concentrate according to claim 1, characterized in that it contains in the aqueous solution (A) sodium carbonate and in the aqueous solution (B) as acid hydrochloric acid.

3. A concentrate according to claim 2, characterized in that it contains in the solution (B) 1,05 to 1,3, preferably 1,05 to 1,2 mole HCl per mole Na_2CO_3 in the solution (A).

4. A concentrate according to claim 2 and 3, characterized in that it contains the sodium chloride and optionally the potassium chloride in the solution (A) and /or the solution (B).

5. A concentrate according to claims 2 through 4, characterized in that up to 0,3 mole-% of the HCl are replaced by acetic acid.

6. A concentrate according to claim 1, characterized in that it contains sodium bicarbonate in the aqueous solution (A).

7. A concentrate according to claim 6, characterized in

that it contains in the solution (B) 0,01 to 0,25, preferably 0,03 to 0,15 mole of the acid per mole of sodium bicarbonate in the solution (A).

8. A concentrate according to claim 6 and 7 characterized in that it contains the sodium chloride and optionally the potassium cations in the solution (A) in a concentration as high as possible.

9. A concentrate according to claims 6 through 8, characterized in that it contains as acid acetic acid, citric acid, lactic acid, hydrochloric acid and/or an amino acid.

10. A concentrate according to claims 6 through 9, characterized in that it contains in the solution (B) additionally glucose, preferably 5 to 400 gs/l, especially 15 to 80 gs/l.

11. A concentrate according to claims 1 through 10, characterized in that it contains the solution (A) in a container which enables no or only a little escape of CO_2 from the solution and the gaseous phase thereover.

European Patent Office

EUROPEAN SEARCH REPORT

Application number
EP 80 10 3136

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
X	US - A - 4 136 708 (COSENTINO) * Abstract, column 1, lines 28-59; column 2, line 64 - column 3, line 36; column 7, line 32 - column 8, line 10 *	1-11
	US - A - 4 085 046 (SAPORITO) * Abstract; column 1, line 64 - column 2, line 4; column 3, lines 25-28 *	1
	FR - A - 1 546 072 (LUCAS) * Page 2, right-hand column, lines 3-29 *	1
	FR - A - 2 237 639 (GENSOLLEN) * Page 3, lines 5-24 *	1
	FR - A - 2 271 864 (SORIN) * Page 3, lines 12-23 *	1
	GB - A - 1 368 566 (VSEZOJUNZNY) * Page 2, lines 43-48 *	1
A	US - A - 3 525 686 (ROBERTS) * Entirely *	1-11

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CLASSIFICATION OF THE APPLICATION (Int. Cl.³)

A 61 M 1/03

TECHNICAL FIELDS SEARCHED (Int. Cl.³)

A 61 M

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

X The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
The Hague	29-10-1980	PESCHEK

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EUROPEAN SEARCH REPORT

Application number
EP 80 10 3136

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	US - A - 3 560 380 (STADE) * Entirely * ----	1-11	TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

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